

## ANESTHETIC COMPOSITION FOR TOPICAL ADMINISTRATION COMPRISING LIDOCAINE, PRILOCAINE AND TETRACAINE

This invention relates to the field of human medicine, and specifically to  
topical anesthetic formulations which include mixtures of several anesthetic  
5 agents.

### BACKGROUND ART

Surgical techniques can only be performed after the highly sensitive nerve  
10 endings in the skin are anesthetized. Anesthetic agents are  
pharmacologically active agents that block nerve impulses conduction in  
sensory and motor nerve fibers when applied in therapeutically effective  
amounts. Their action is reversible, their use being followed by the complete  
recovery in nerve function with no evidence of structural damage to nerve  
15 fibers or cells.

To be effective, a topical anesthetic should contain sufficient concentration of  
the active agent to produce an anesthetic effect, it should penetrate intact  
skin sufficiently to deliver a therapeutic dose, it should exhibit a rapid onset of  
20 anesthetic action and have a prolonged anesthetic effect. Potency of  
anesthetics in clinical situations depends on both their ability to reach the  
nerve fibers and their intrinsic blocking activities. Factors such as nerve  
penetration, vascular absorption, and local tissue binding are all of them  
determinants for anesthetic potency.

25 Local anesthetics are traditionally injected into the desired site with a syringe.  
Most formulations of local anesthetics are aqueous solutions designed for  
injection into tissue, around nerves, or into the epidural spaces. The use of  
syringe is disadvantageous because the needle itself causes pain on  
30 penetration, the volume of anesthetic dissolution can cause stretching at the  
site (also causing pain), and furthermore preservatives contained in the  
aqueous dissolution can cause stinging at the wound site. Pain relief is  
especially important in the area of pediatrics, where even minimal pain may  
result in an anxious and uncooperative patient.

35 It is known the use of topical anesthetics. Transdermal delivery is  
advantageous over intravenous delivery because the former avoids risks

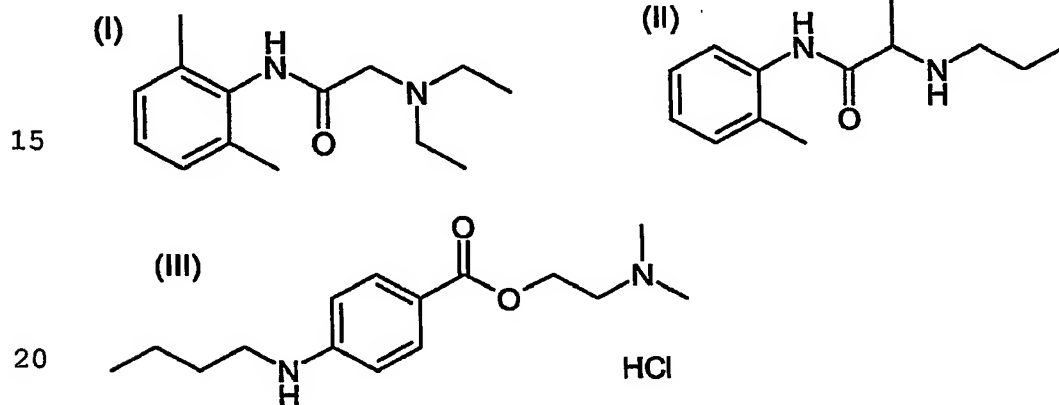
associated with parenteral treatment and eliminates gastrointestinal adverse effects due to pharmaceutical active ingredients, preservatives, etc. However, the use of transdermal anesthetics (i.e. through the skin) is often problematic, and fluid and in gel compositions have often proven unsuccessful.

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The amide of formula (I), known as lidocaine, has a melting point of 68-69 °C and it is the most commonly used local anesthetic, especially in the form of aqueous dissolutions of its hydrochloride, which are administered intravenously or topically, as jelly, ointment or spray (cf. US 2.441.498).

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Unfortunately, when administered topically, these formulations are not effectively absorbed transdermally, but only through mucosal surfaces.



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The amide of formula (II), known as prilocaine, is a local anesthetic agent which takes the form of crystalline needles having a melting point of 37-38 °C (cf. GB 839.943-A). Its hydrochloride is crystallized from ethanol and isopropyl ether and it is readily soluble in water. Unfortunately, methemoglobinaemia and cyanosis appear to occur more frequently with prilocaine than with other local anesthetics. Methemoglobinaemia is a disease state of the erythrocyte consisting in the formation of oxidized iron compound in the heme protein of the erythrocyte. Symptoms usually occur when doses of prilocaine hydrochloride exceed about 8 mg per kg body-weight although the very young may be more susceptible. This fact severely limits the size of the area to be anesthetized.

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Enhancement of drug absorption through the skin has been a challenge for researchers for many years. Research has been also focused on finding

effective topical formulations of an anesthetic which provide a rapid onset and a long duration of anesthesia. When applied onto intact skin, currently available topically used anesthetic preparations are generally ineffective or only partially effective.

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One approach to the prolongation of anesthesia involves the combination of topical anesthetics with a vasoconstrictor, but also involves considerable adverse side effects. Another approach involves the combination of several anesthetic agents and different topical excipients (cf. e.g. EP 43.738-A, WO 10 9633706-A). In fact, at present, the most successful commercially available preparation for dermal anesthesia is the lidocaine-prilocaine cream named EMLA (a registered trademark in some countries) of Astra Lakemedel AB, Sweden (cf. US 4.562.060). In some clinical tests, EMLA cream has been found preferable to lidocaine or to ethylchloride. EMLA is an oil-in-water 15 emulsion in which the organic phase is an eutectic mixture of lidocaine and prilocaine bases (2.5% and 2.5% by weight) in water which is thickened with carbomer (Carbopol®). An eutectic mixture has a melting point lower than the one of any of its ingredients. EMLA cream is applied as a thick layer under an occlusive or semioclusive dressing for inducing a rapid absorption through 20 the skin.

A major inconvenience of EMLA is that its onset time for anesthesia is relatively long, approximately one hour or more. This onset time is not very practical for several clinical procedures. For more invasive procedures such 25 as split skin graft harvesting, EMLA has to be applied at least two hours prior to surgical operation. Such delay is a problem for both patients and for medical staff, particularly in the area of pediatrics. Moreover, EMLA is formulated at pH 9.0 to incorporate the anesthetic agents in base form. The skin, which has an acidic pH (5 to about 5.5) is sensitive to such a high basic 30 pH and significant skin irritation can occur. Dermal application of EMLA may cause a transient, local blanching followed by a transient, local redness or erythema. Another disadvantage of EMLA is that for deep penetrative effect it is necessary that the cream is applied under occlusive dressing.

35 There have been several attempts trying to improve EMLA cream. One example are topical anesthetic compositions which additionally include a vasodilator. A formulation including lidocaine base, prilocaine hydrochloride,

dibucaine, a vasodilator and carrier is described in the patent application WO 01/54679-A. Another example is the topical anesthetic composition comprising an eutectic mixture of lidocaine and prilocaine in a lipophilic base described in the US patent 5.993.836. It has been reported that this  
5 anesthetic formulation has significantly more rapid onset than similar transdermal anesthetics, such as EMLA cream.

Tetracaine hydrochloride (amethocaine) is a local anesthetic of the ester type with formula (III) (cf. US 1.889.645). There are many topical formulations in  
10 the market containing tetracaine hydrochloride, one of them is AMETOP of T.J. Smith & Nephew Limited, England (cf. GB 2.258.397-A) which contains 40 mg of active ingredient (4%, w/w), an aqueous gelling agent and a pharmaceutically acceptable salt.

15 Thus, it appears to be highly desirable to have a topical anesthetic composition which provides a rapid and deep anesthesia, with a high concentration on skin. In particular, it would be desirable to have a topical anesthetic with the benefits of lidocaine and prilocaine, but free of the above-described limitations associated therewith.

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## SUMMARY OF THE INVENTION

It has now been surprisingly found that a topical anesthetic composition comprising a mixture of lidocaine, prilocaine and tetracaine, exhibit a  
25 significantly more rapid onset of the anesthetic effect than comparable transdermal anesthetics, such as EMLA cream.

Thus, an aspect of the present invention relates to a pharmaceutical composition for topical administration comprising: (i) a therapeutically safe  
30 and effective amount of lidocaine or of a pharmaceutically acceptable salt thereof; (ii) a therapeutically safe and effective amount of prilocaine or of a pharmaceutically acceptable salt thereof, and (iii) a therapeutically safe and effective amount of tetracaine or of a pharmaceutically acceptable salt thereof.

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In a particular embodiment the composition further comprises water. When tetracaine is as its hydrochloride, it can be dissolved in water and added to

the previously prepared mixture of lidocaine and prilocaine. When tetracaine is as such, water is not necessary, so tetracaine can be added to the mixture of lidocaine and prilocaine directly. Optionally, the mixture of lidocaine, prilocaine and tetracaine can also be dissolved in alcohols (e.g. ethanol, isopropanol and mixtures thereof).

In another embodiment, lidocaine or its salt on the one side, and prilocaine or its salt on the other side, form an eutectic mixture. As an eutectic mixture, the compositions remain liquid at room temperature and the penetration through the skin is enhanced, giving as a result, a shorter time of effect establishment, a higher efficacy and less adverse effects. Particularly, lidocaine or its salt can be in an amount from about 0.5% to about 5%, w/w, and prilocaine or its salt can be in an amount from about 0.5% to about 5%. More particularly, lidocaine, prilocaine, or their salts are in an amount of about 1.5%, w/w. On the other hand, tetracaine or its salt can be in an amount from about 0.5% to about 8%, w/w, and more particularly, in an amount of about 4%, w/w.

In another embodiment, the pharmaceutical composition further comprises appropriate amounts of pharmaceutically acceptable excipients to constitute a topical formulation. The composition can comprise different types of excipients: skin penetration enhancers, spreading agents, viscosity increasing agents, surfactants and preservatives. Optionally, other components can be added to the compositions of this invention in appropriate amounts to enhance their pharmaceutical acceptability, as it will be obvious to a person skilled in the art.

The composition can comprise at least one skin penetration enhancer which enhances dermal absorption of the active ingredients by reversibly altering the barrier of skin. Preferred skin penetration enhancer agents that may be used are dipolar aprotic solvents as methylpyrrolidone and dimethyl sulfoxide (DMSO) which are rapidly absorbed through the skin and enhance dermal absorption of many other chemicals. In a particular embodiment, methylpyrrolidone is in an amount from about 5% to about 20%, w/w. In a more particular embodiment, methylpyrrolidone is in an amount of about 10%, w/w. In another particular embodiment, the skin penetration enhancer is dimethyl sulfoxide (DMSO), which is in an amount from about 0.5% to about 5%, w/w, and more particularly in an amount of about 2%, w/w.

The composition can comprise at least one spreading agent, which facilitates uniform spread of anesthetic agents. In particular embodiments, the spreading agent is selected from hyaluronidases and/or derivatives of mucopolysaccharidases. They prevent the elevation of extracellular tissue pressure and also prevent focal accumulations of local anesthetic agents, which at high enough levels may cause neurotoxic damage.

The composition can further comprise at least one viscosity increasing agent, also known as thickening agents. Thickeners that may be used include those known to one skilled in the art, such as hydrophilic and hydroalcoholic gelling agents frequently used in cosmetics, food products and pharmaceutical formulations. Preferably, a commercial carbomer will be used, Carbopol N-940. Another preferred gelling polymer includes guar gum. In particular embodiments, the viscosity increasing agent is in an amount from about 0.5% to about 2%, w/w.

The composition can comprise at least one surfactant, also known as emulsifier. These compounds are widely used in the preparation of stable pharmaceutical, cosmetic and food emulsions. In a preferable embodiment the surfactant is a non-ionic surfactant and in a more particular embodiment, polysorbates are used (e.g. polysorbate 20 and 80).

The compositions of the present invention may be prepared and packaged under sterile conditions. Alternatively, at least one suitable antimicrobial agent may be incorporated into the formulations as preservatives. Some known preservatives useful in this invention include methylparaben and propylparaben in their acidic form or as sodium salts.

The topical formulations of the present invention may be made into a wide variety of product forms, as it is well known in the art. These include, among others, lotions, creams, gels, sticks, sprays, ointments and pastes. In order to facilitate the application of the compositions, they can be, for instance, in a dispenser or on the surface of a dressing, a patch or a pad. These product forms may comprise several types of carriers including, among others, dissolutions, aerosols, emulsion gels, solids and liposomes.

Another aspect of the present invention relates to a pharmaceutical composition for topical administration comprising the following components in the indicated approximate w/w percentages: 1.5% of lidocaine base; 1.5% of prilocaine base; 4% of tetracaine base; 10% of methylpyrrolidone; 2% of  
5 dimethyl sulfoxide; 0.08% of topical hyaluronidase; 1.5% of guar gum; 1% of Tween-20; 0.5% of Tween-80, and the necessary amount of water to 100%.

The application of the compositions of the present invention comprises contacting an area of skin with a thin layer of the composition. When an  
10 intravenous device is used, the application of the compositions of the present invention will be preferably at its site of insertion. The composition is allowed to act for an appropriate time for the onset of anesthesia. The term "onset of anesthesia" means the time until peak effect on the nerve endings. For the compositions of the present invention, this time is shorter than with other  
15 commercial compositions. In a preferred method of using, three consecutive applications may be done: a first application followed by ten minutes of resting to achieve the anesthetic effect; a second application followed by ten minutes more, and a third application followed by five minutes of resting. After these twenty-five minutes in all, the composition can be removed and the  
20 surgical operation can be done or the medical device can be inserted. The duration of anesthetic effect for the compositions of the present invention is from about one to about five hours, depending on the subject metabolism. The effect is much more durable and increases in time compared with other available compositions.

25 In addition to the rapid onset, the formulations of the present invention are advantageous for not depending on the application of an occlusive or a semioclusive dressing for getting a rapid absorption through the skin. Even if it is not necessary, occlusion may be applied. The compositions of the  
30 invention may be applied directly to the skin or by the use of transdermal treatment systems, including patches or pads, which are semipermeable membranes with the active compound applied to the surface.

The compositions of the present invention are particularly useful before  
35 superficial dermatological treatments. These include, among others, surface verruca extirpation, infiltrations or molluscum extraction. The same applies before esthetic treatments such as peelings, filling micropuncture of wrinkles,

laser or application of facial filling; and before the insertion of a medical device.

5 The term "safe and effective amount" as used herein, means an amount of an active ingredient or a composition high enough to deliver the desired skin benefit, but low enough to avoid serious side effects within the scope of medical judgment. The term "pharmaceutically acceptable" as used herein, means suitable for use in contact with the tissues without undue toxicity, irritation, incompatibility, instability, allergic response, and the like. All  
10 numerical ranges used herein, are meant to be inclusive of their upper and lower limits. Unless noted otherwise, all percentages in the compositions of the invention are on a weight-to-weight basis. Throughout the description and claims the word "comprise" is not intended to exclude other technical features, additives, components, or steps. The abstract of this application is  
15 incorporated herein as reference. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following particular embodiments are provided by way of illustration, and is not intended to be limiting of the present invention.

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## DETAILED DESCRIPTION OF PARTICULAR EMBODIMENTS

### Preparation of the composition

25 Tubes of 30 g were prepared with the composition per tube described in the following table:



Component	% (w/w)
<b>Dissolution A</b>	
Distilled water	31.82%
Nipagin M-Ac	0.08%
Nipasol M-Ac	0.02%
Tween-20	1.00%
Guar gum	1.50%
<b>Dissolution B</b>	
Tetracaine HCl	4.00%
Distilled water	45.00%
<b>Dissolution C</b>	
Lidocaine base	1.5%
Prilocaine base	1.5%
<b>Dissolution D</b>	
Distilled water	1.00%
Topical hyaluronidase	0.08%
<b>Dissolution E</b>	
Tween 80	0.50%
<b>Dissolution F</b>	
Methylpyrrolidone	10%
<b>Dissolution G</b>	
DMSO	2.00%

Lidocaine base and prilocaine base were weighed and sieved through a 2 mm mesh. Components of dissolutions A, B, D, E, F and G were weighed separately. The amounts of required distilled water for each dissolution were also prepared in 100 mL recipients. Distilled water for dissolution A was heated in an appropriate recipient and Nipagin and Nipasol were added until dissolved. The mixture was left to cool. Then, Tween-20 was added and the mixture was shaken with a stripping knife without lathering. Guar gum was added to the mixture and shaken during ten minutes with a glass stick. In the 100 mL recipient containing distilled water, tetracaine HCl was added and it was dissolved with a magnetic agitator during fifteen minutes at a regular speed. Tetracaine dissolution was added over dissolution A and shaken during ten minutes until homogenized. Lidocaine base was mixed with prilocaine base in a mortar during fifteen minutes until obtaining the

liquefaction and consequently the total fusion of the eutectic mixture. The eutectic mixture was added over the preceding mixture and shaken during ten minutes until complete homogenization. The resulting product was transferred to a 100 mL recipient. Hyaluronidase was mixed with the  
5 corresponding amount of distilled water and shaken with a glass stick. This dissolution was added to the preceding mixture. Dissolution E, F and G were finally added consecutively and shaken until complete homogenization. The 30 g of the resulting product was transferred to an aluminum tube.

10 Comparative clinical study between a topical anesthetic composition of the invention and EMLA cream: efficacy and adverse effects

The aim of the study was to compare the efficacy between a topical anesthetic composition of the invention versus EMLA cream. Adverse effects  
15 of both compositions were also evaluated. The study was executed during two years over a 2700 individual population with ages comprised between fifteen and sixty-five years. Different superficial dermatological procedures were made such as surface verruca extirpation, infiltrations, application of facial filling, laser or filling micropuncture of wrinkles.

20 The topical anesthetic composition of the invention was applied to the half of the population during thirty minutes previous to the surgical operation and without occlusion. EMLA was applied to the other half of the population during sixty minutes previous to the surgical operation and with occlusion. The  
25 degree of pain was evaluated by the patient himself with a visual analogous scale (VAS) with a minimum value (equivalent to no pain) "0" and a maximum value (equivalent to maximum pain) "10". The degree of pain was evaluated during the execution of the dermatological procedure while the evaluation of adverse effects emergence was evaluated from the anesthetic application to  
30 the end of the dermatological procedure.

Table 1 shows the results in terms of anesthetic efficacy.

Tables 2 and 3 shows the results of the evaluation of adverse effects emergence during and after the application of both creams. Table 2 shows  
35 the results in terms of adverse effects of the composition of the invention and table 3 in terms of adverse effects of EMLA. In both cases few patients with adverse effects were registered, although in the case of EMLA these effects

were more acute and in the case of the composition of the invention the effects were softer, of short length and with spontaneous resolution.

Table 1											
degree of pain (VAS)	0	1	2	3	4	5	6	7	8	9	10
EMLA	-	-	338	270	135	270	135	135	135	-	-
the composition of the invention	702	162	149	162	108	67	-	-	-	-	-
total patients	2700										

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Table 2				
adverse effects	null	soft	moderate	severe
erythema	89%	10%	1%	0
edema	99%	1%	0	0
itching	90%	10%	0	0

Table 3				
adverse effects	null	soft	moderate	severe
erythema	92.5%	0	7.5%	0
itching	97.5%	0	2.5%	0
cutaneous rash	100%	0	0	0

From the results shown in the tables, it is clear that the composition of the invention proves a larger efficacy and a shorter time of effect establishment versus EMLA for the same type of dermatological and/or dermoesthetic procedure. The effectiveness of EMLA is practically the half with a double time of application.

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